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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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09/840,277

04/23/2001

Ulrich Feige

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21069

7590

04/10/2007

AMGEN INC.

MAIL STOP 28-2-C

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EXAMINER

WESSENDORF, TERESA D

ART UNIT

PAPER NUMBER

1639

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
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3 MONTHS

04/10/2007

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No. 09/840,277	Applicant(s) FEIGE ET AL.	
	Examiner T. D. Wessendorf	Art Unit 1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 07 February 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 26 and 28-45 is/are pending in the application.
- 4a) Of the above claim(s) 26, 36-43 and 45 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 26, 28-35 and 44 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/7/2007 has been entered.

Election/Restrictions

Newly submitted claims 36-43 and 45 directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: these species have been withdrawn from consideration in the last Office action. Accordingly, these claims have not been examined on the merits.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 36-43 and 45 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

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Status of Claims

Claims 26 and 28-45 are pending in the instant application.

Claims 26 (with respect to the other non-elected species), 36-43 and 45 are withdrawn from further consideration as being drawn to non-elected species.

Claims 26, 28-35 and 44 are under examination.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 26, 28-35 and 44, as amended, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claim 26 is unclear and confusing. Is the definition of P1-P4 as "each independently selected from RGD and Seq. ID. Nos. 7 and 128 to 137" means that each of P1-P4 is selected from any one of RGD, Seq. ID. No. 7 or Seq. ID. 128-137? Or that each of P1-P4 is selected with RGD in combination with the different sequences? Clarification is required. (It is suggested that

applicants employ the Markush language in the selection of the sequences).

B. Claim 32 is a duplicate of claim 31.

C. Claim 35 language "wherein any of P1, P2, P3 and P4 is independently Seq. ID. No. 7" is unclear and confusing, especially in the absence of positive support in the specification. This rejection has similar import to claim 44.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 103

Claims 26 and 28-35, as amended, are rejected under 35 U.S.C. 103(a) as being unpatentable over Whitty in view of Mu and Liu et al (6,835,809) for reasons as reiterated below.

Whitty discloses at page 3, lines 1-27 an isolated polypeptide having the amino acid sequence X--Y--Z, wherein X is a polypeptide having the amino acid sequence, or portion thereof, consisting of the amino acid sequence of interferon beta; Y is an optional linker moiety; and Z is a polypeptide comprising at least a portion of a polypeptide other than interferon beta. Optional moiety Y and required moiety Z may be linked to either the N- or C-terminus of interferon beta (X). Preferably, X is human interferon-beta-1a. Z is at least a portion of a constant region of an immunoglobulin and can be

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derived from an immunoglobulin of the IgG class such as IgG1, IgG2, IgG3 and IgG4. See Fig. 3, page 5. Whitty further discloses at paragraph bridging pages 19 and 20, that in the fusion proteins, the interferon-beta-1a polypeptide is fused via its C-terminus to at least a portion of the Fc region of an immunoglobulin. The interferon-beta-1a forms the amino-terminal portion, and the Fc region forms the carboxy terminal portion. Whitty describes at page 20, line 24 up to page 21, line 15, a dimeric fusion molecules as well as monomeric or multimeric molecules comprising fusion proteins. Such multimers may be generated by using those Fc regions, or portions thereof, of Ig molecules which are usually multivalent such as IgM pentamers or IgA dimers. Multimers of interferon-beta-1a fusion proteins may be formed using a protein with an affinity for the Fc region of Ig molecules. The polyvalent forms are useful since they possess multiple interferon beta receptor binding sites. For example, a bivalent soluble interferon-beta-1a may consist of two tandem repeats of amino acids 1 to 166 of SEQ ID NO: 2 (moiety X in the generic formula) separated by a linker region (moiety Y), the repeats bound to at least a portion of an immunoglobulin constant domain (moiety Z). Alternate polyvalent forms may also be constructed, for example, by chemically coupling interferon-

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beta-1a/Ig fusions to any clinically acceptable carrier molecule like polyethylene glycol using conventional coupling techniques.

Whitty fails to disclose a fusion protein with laminin of the sequence YIGSR and poly(gly-ala) as the linker. However, Mu discloses that laminin peptide with YIGSR bioconjugated with polystyrene co-maleic acid results in increase of antimetastatic effect. See page 75, col. 1 and 2. Mu further discloses that to be therapeutically useful YIGSR peptide requires in vivo stability that allows administration of YIGSR. Mu discloses similar bioconjugation of other extracellular matrix domains, besides YIGSR, such as Interferons. Mu discloses that alone, without any carrier, the small size YIGSR undergoes degradation (cf. with the same conclusive finding in the disclosure). Liu discloses at col. 6, line 38 that natural amino acids linker such as polygly in combination with any one of the other 19 natural amino acid render the synthesis of the conjugate(col. 4, line 25 up to col. 5, line 24) accessible to recombinant technologies. See also, col. 10, lines 32-61. Liu further discloses at col. 11, line 7 that a non-peptide linker as polyethylene glycol can also be used as a linker. It would have been obvious to one having ordinary skill in the art at the time the invention was made to replace the interferon in the fusion protein composition of Whitty with a YIGSR-containing laminin,

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as taught by Mu. Mu teaches that laminin and interferon belong to the family of extracellular matrix domains (active in adhesion). It would be within the ordinary skill in the art to pick or choose the specific compounds from the family of extracellular matrix domain compounds. Fusion of these peptides to Fc with the extracellular domain compounds, results in increased in vivo stability relative to the non-fused peptide. Such in vivo stability would motivate one having ordinary skill in the art. In vivo stability is an important aspect for therapeutic effect of a compound agent in the treatment of any disease particularly, tumors. To substitute the PEG linker in the composition of Whitty with a natural amino acid linkers as poly(gly-ala) as taught by Liu would have been obvious to one having ordinary skill in the art at the time the invention was made. Liu teaches that these linkers are functionally equivalent linkers but poly(gly-ala) being a natural amino acids renders the synthesis of the conjugate accessible to recombinant technology. This benefit would provide one having ordinary skill in the art to make said linker substitution. Accordingly, the combined teachings of the prior art render the claimed composition prima facie obvious at the time of applicants' invention.

Response to Arguments

Applicants state that nothing in the cited references would lead one skilled in the art to any YIGSR repeat Fc molecule or any of the other molecules recited in Claim 26 (or in new Claims 28-45) in particular, i.e., where "P2, P3, and P4 are each independently selected from RGD and SEQ ID NOS: 7 and 128 to 137."

In response, applicants' arguments as to the YIGSR repeat Fc molecule is not commensurate in scope with the claims, which do not recite any repeat(s).

Applicants state that the Examiner has acknowledged that SEQ ID NO:136 (e.g., Claims 26 and new Claim 44) is free of the prior art, and has failed to present a prima facie case of obviousness as to any of the peptide (P) sequences recited in Claim 26, or by extension in new dependent Claims 28-45.

In response, that claim 44 is free of prior art is not controverted. Claim 26, as applicants acknowledged contain other P definitions beside Seq. ID. 136.

Applicants alleged that the Examiner further fails to point to any suggestion to combine the teachings of the three references, relying instead on a hindsight reconstruction using the application itself as a guide.

In response to applicants' argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). Attention is again directed to the above combination of references and the motivation provided to one having ordinary skill in the art to make the modifications to arrive at the claimed composition.

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Applicants asked to consider that, contrary to obviousness, neither the cited references nor the general knowledge in the art would have predicted the results disclosed in the above-captioned application as to a laminin-Fc fusion comprising a P of (YIGSR)₃ [SEQ ID NO:129] (e.g., Claim 26 and new Claim 37)--a greater than 50-fold enhancement in activity, from the low micromolar range (IC₁₀₀ of 2.9 IJM) for the naked synthetic peptide to the low nanomolar range (IC₁₀₀ of 55 nM), when it was coupled to Fc (specification as originally filed, at page 57, lines 7 to 9)

In reply, applicants' arguments that the argued claim Seq. ID. 129 having a 50-fold enhancement are not commensurate in scope with the claims since claim 37 is withdrawn from consideration. [It is unclear how applicants can argue about the unpredictability of the prior art sequences when claim 26, which contains other sequences besides Seq. ID. 29 has not also predicted an enhancement in activity].

As indicated in the previous Office action Seq. ID. 136, i.e., claim 44 is free of prior art.

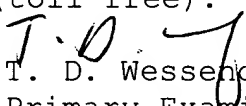
No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to T. D. Wessendorf whose telephone number is (571) 272-0812. The examiner can normally be reached on Flexitime.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).


T. D. Wessendorf
Primary Examiner
Art Unit 1639

Tdw
March 31, 2007